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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,314	04/19/2006	Christoph Hock	78247/JPW/YC	2670

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EXAMINER	
WANG, CHANG YU	
ART UNIT	PAPER NUMBER
1649	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,314	HOCK ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11-17 and 19* is/are pending in the application.

4a) Of the above claim(s) *11-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/27/09 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendments filed 2/27/09 & 4/27/09 are acknowledged. Claims 2-10 and 18 are cancelled. Claim 1 is amended. Claim 19 is newly added. Claims 1, 11-17 and newly added claim 19 are pending in this application. Claims 11-17 are withdrawn without traverse (the response filed on 6/1/07) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 1 and 19 are under examination in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this office action, has been overcome by Applicant's response.

5. Applicant's arguments filed on 2/27/09 & 4/27/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

6. The rejection of claims 1, 4-7 and 18 under 35 U.S.C. 112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is withdrawn in response to Applicant's amendment to the claims and cancellation of claims 4-7 and 18.

Claim Rejections/Objections Maintained

In view of the amendment filed on 2/27/09 & 4/27/09, the following rejections are maintained.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dodel et al. (EP1172378, published on Jan 16, 2002 cited in the previous office action)

in view of Schenk et al. (Nature. 1999. 400: 173-177 cited in the previous office action) and US Patent No. 5898094 (Duff et al., issued Apr 27, 1999). The rejection is maintained for the reasons made of record, and as follows.

On p.6-8 of the response, Applicant argues that neither Dodel nor Schenk teaches the use of brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice in a method of monitoring and prognosticating the clinical outcome of an immunotherapy in a human subject suffering from Alzheimer's disease and being immunized against pre-aggregated Aβ1-42. Applicant argues that the level of anti-Aβ antibody is detected in samples from patients who have been passively immunized with human IgG or anti-Aβ antibody not Aβ1-42 as recited in instant claims. On p. 8-9 of the response, Applicant argues that Schenk does not teach that animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques and does not teach that anti-Aβ antibodies can recognize Aβ plaques on brain tissue. Applicant argues that a skilled artisan would not know the transgenic PDAPP animals may be useful in monitoring an immunotherapy in a subject suffering from AD. Applicant's arguments have been fully considered but they are not persuasive.

In response, as previously made of record, Applicant cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In contrast, the examiner asserts that the applied references do render the claimed method obvious. In this case, Dodel (EP'378) teaches detection of the levels of

anti-Aβ antibodies and Aβ peptides in plasma and CSF as compared to controls or before treatment (i.e. comparing the level of immunoreactivity between a test sample and an amyloid plaque-containing sample) as in instant claims 1 and 19 (see col.3 [0019]; col. 6 [0038]). Although Dodel does not teach contacting serum or CSF with brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice to detect the level of anti-Abeta antibodies, the use of brain sections containing amyloid-plaques or brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice to monitor immunotherapy is obvious over the teachings of Dodel, Schenk and US Patent No. 5898094.

Schenk teaches detection of a reduction of amyloid plaques by immunohistochemical staining on the brain sections of the immunized PDAPP mice as compared to those of non-immunized PDAPP mice (see p. 176-177). PDAPP mice are an AD animal model that carries a human APP minigene with the V717F mutation and this mutant APP causes accumulation of amyloid deposits. The detection of reduced amyloid plaques in immunized PDAPP mice as compared to non-immunized mice indicates that the antibodies generated from Abeta immunization can recognize amyloid plaques and thus a higher level of staining of Abeta can be detected on brain sections of the non-immunized mice (see p. 174-175, in particular). Schenk also teaches detection of increased levels of anti-Abeta antibodies in serum or CSF of transgenic PDAPP mice immunized with Abeta peptides (see p. 174-175, in particular).

US Patent No. 5898094 (the '094 patent) teaches that the $APP^{SW}xPS1^{M146L}$ double transgenic mice is an AD model that has enhanced and accelerated amyloid accumulation (see col. 4,lines 1-50; col. 7-8; col. 9, lines 4-col.12, table 1, in particular).

The $APP^{SW}xPS1^{M146L}$ double transgenic mice carry the Swedish mutation transgene, (i.e. APP695 isoform containing a K670N&M671L mutation) and the PS1 M146L mutation transgene (see col. 4, lines 1-50, in particular). The '094 patent teaches that the $APP^{SW}xPS1^{M146L}$ double transgenic mice have more Abeta deposits and AD phenotypes as compared to APP (APPK670N, M671L) transgenic mice or PS1M164L mice (see col.10-12, table 1, in particular).

Although Dodel and Schenk do not directly use the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice to detect the levels of anti-Abeta antibodies in immunized mice, it is expected to detect higher levels of amyloid-plaques on the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice and thus use this detection method as an indicator of immunotherapy because the levels of anti-Abeta antibodies from patients or animals with Abeta immunization are increased in serum and CSF. In addition, the anti-Abeta antibodies generated from Abeta immunization can recognize the epitopes of Aβ (immunogen) on the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice because the $APP^{SW}xPS1^{M146L}$ double transgenic mice carry APP^{SW}, which is the gene that increases amyloid processing and accumulation, and $PS1^{M146L}$, which the gene that causes production of a greater amount of Abeta (see col.1-3, in particular). Thus, the increased immunoreactivity after immunization with Abeta as compared to prior to immunotherapy on the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice is expected when the brain sections are contacted with the serum or CSF derived from animals or patients immunized with Abeta and thus to be used to monitor the efficacy of immunotherapy.

Accordingly, the claimed method as recited in instant claims are obvious over the applied references because animals or patients immunized with Aβ generate anti-Aβ antibodies against Aβ plaques and show reduced Aβ burden and because the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice show significant increased amyloid accumulation and AD phenotypes. Thus, a skilled artisan would have expected success in monitoring an immunotherapy in a subject suffering from AD by using the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice as a tool to detect the anti-Abeta level after immunization because the detection of higher levels of amyloid-plaques on the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice is expected and the increased level of anti-Abeta antibodies in AD immunized with Abeta has been shown to reduce Abeta burden as taught by Schenk and Dodel, which is as an indicator of improvement of the immunotherapy in AD.

Note that it would have been obvious by combining prior art elements according to known methods to yield predictable results because all the claimed elements were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods, which is applied to the instant application. In addition, it is also obvious by applying a known technique to a known product ready for improvement to yield predictable results because a particular known technique was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product that was ready for improvement and the results would have been predictable to

one of ordinary skill in the art, which is also applied to the instant invention. See KSR International Co. v. Teleflex Inc. 82 USPQ2d 1385 (2007).

In addition,

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

On p. 10-12 of the response, Applicant argues that Schenk does not teach a positive correlation of the level of anti-Abeta antibodies in serum and CSF after treatment or immunized with Abeta. Applicant argues that Schenk does not teach that the level of anti-Abeta indicates the outcome of neuropathology in terms of Abeta burden and amount of plaque deposits in the brain. Applicant argues that the present invention is a better indicator of a positive clinical outcome in AD immunotherapy than the conventional ELISA method because high levels of immunoreactivity as determined by the claimed method show beneficial clinical effects as compared to the ELISA method. Applicant further cites Sabamurti et al. in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, as previously made of record, both Dodel and Schenk teach methods of monitoring immunotherapy by detecting the level of anti-Abeta with an ELISA method. In addition, Schenk teaches image analysis on brains sections containing amyloid plaques to determine amyloid-β burden after immunization with Abeta (see p. 176, in particular), which is immunohistochemical analysis on the brain sections to monitor immunotherapy. Schenk further teaches that the reduction of Abeta accumulation in immunohistochemical analysis in animals immunized with Abeta

peptides correlates with the increased levels of anti-Abeta and the effect of anti-Abeta (see p. 176, in particular). Thus, both Dodel and Schenk teach methods of detecting and assessing clinical outcome of immunotherapy of Abeta immunization. Although Dodel and Schenk do not teach the use of the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice as a tool to detect the anti-Abeta level after immunization, it is obvious to use the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice as a tool to detect the anti-Abeta level after immunization because the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice show more accelerated and significant increased amyloid plaque accumulation and AD phenotype. Thus, the result of using the brain sections of the $APP^{SW}xPS1^{M146L}$ double transgenic mice as a tool to detect the anti-Abeta level after immunization is expected.

Note that

"A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." *In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). See MPEP 716.02(a)-I.

Conclusion

8. NO CLAIM IS ALLOWED.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Holcomb et al. (Nat. Med. 1998 Jan; 4:97-100) teach that accelerated Alzheimer-type phenotype can be found in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes.

Gordon et al. "Correlation between cognitive deficits and Abeta deposits in transgenic APP+PS1 mice". (Neurobiol. Aging. 2001. 22: 377-386) teach that APPswe+PS1M146L double transgenic mice develop more deficits in cognitive ability and Abeta deposits.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
June 16, 2009

/Christine J Saoud/

Primary Examiner, Art Unit 1647